Hepatocellular carcinoma (HCC) is the fifth most common neoplasm worldwide and a major cause of cancer-related death. The development of HCC has long been associated with inflammation-causing agents such as chronic viral infection with hepatitis B or C, alcoholic cirrhosis, or dietary exposure to fungal aflatoxins (1–3). Consequently, HCC progression unravels against a backdrop of persistent inflammation, extensive tissue remodeling, and excessive deposition of extracellular matrix components (2–4). Moreover, recently gained insights have linked inflammation to the aberrant activation of a latent embryonic program—termed the epithelial–mesenchymal transition (EMT)—that endows tumor cells with metastatic competence (5–7) and resistance to therapy (8). EMT is a complex process that enables the reprogramming of polarized epithelial cells toward a mesenchymal phenotype accompanied by shedding of epithelial characteristics, loss of apico-basal polarity, dissolution of intercellular contacts, and gain of intrinsic migratory and invasive capabilities (7).

Both persistent inflammation and EMT have been independently implicated in wound healing and regeneration following tissue injury and in pathological conditions such as organ fibrosis and metastasis (7,9,10). Indeed, the induction of an inflammatory response plays dual and opposing roles in the context of tumor development. Initially, inflammation and immune surveillance serve to eliminate rogue premalignant or malignant cells, thus suppressing tumor formation. However, as tumors evolve, they not only evade immune surveillance but—somewhat paradoxically—provoke an inflammatory response, resulting in the recruitment of multiple immune cell types that secrete a diverse set of signaling molecules that promote cell proliferation and survival of resident cells and remodel the extracellular matrix to favor EMT. Accordingly, several inflammatory stimuli have been shown to activate and stabilize EMT-inducing transcription factors, thus providing a molecular basis for the links between inflammation and the EMT process (9,11).

In this issue of the Journal, Ai et al. (12) identify the polymeric immunoglobulin receptor (pIgR)—a key inflammatory mediator—as a prognostic biomarker for HCC and a molecular player in hepatitis B infection, chronic liver inflammation, the induction of EMT, HCC recurrence, and metastatic progression. Whereas pIgR aberrant expression has long been associated with HCC (13), its relevance to malignancy has remained unclear. Thus, to date, the only known function of pIgR is in mediating transcytosis of polymeric immunoglobulins from the basolateral to the apical surface of epithelia, ultimately facilitating the secretion of IgA and IgM, which comprise the first-line of defense against infection (14).

The study by Ai et al. (12) reveals previously unrecognized roles for pIgR by demonstrating that pIgR overexpression is capable of eliciting EMT in MDCK cells as well as in immortalized or transformed hepatic cell lines. Conversely, pIgR–small hairpin RNA knockdown restored epithelial characteristics in tumor necrosis factor-α–treated HT29 cells and MDCK cells ectopically expressing pIgR. In vivo, pIgR-overexpressing cells yielded a higher number of experimental lung metastases compared with control counterparts, confirming that pIgR overexpression can promote colonization. Consistent with EMT, Ai et al. (12) detected decreased levels of epithelial markers (E-cadherin, cytokeratins) and increased levels of the mesenchymal marker, vimentin, and phospho-Smad2/3 in pIgR-overexpressing HCC specimens.

At the mechanistic level, Ai et al. (12) implicate pIgR in the EMT initiated by cross talk of transforming growth factor-β (TGF-β) with inflammatory mediators (tumor necrosis factor-α, interferon-γ, interleukin-4). Thus, they demonstrated that pIgR overexpression enhances Smad2/3 nuclear translocation following TGF-β/cytokine treatment and identified pIgR as a novel partner of the Smad complex that activates Smad signaling by recruiting Smad2.

It is well established that TGF-β functions as a tumor suppressor early in tumorigenesis, whereas in later stages of carcinogenesis, it exacerbates tumor progression by promoting immune evasion and angiogenesis (15,16). Furthermore, loss of key TGF-β signaling mediators (eg, Smad4) enables tumor cells to become refractory to cytostasis and primed for EMT (16). For example, Battaglia et al. (17) showed that the hepatitis C virus core protein decreases Smad3 activation in hepatocytes, switching the TGF-β response from cytostasis to EMT. The study by Ai et al. (12) is the first demonstration of a host immunoglobulin receptor that synergizes with TGF-β/Smad signaling and the inflammatory milieu to engage EMT, thus bestowing metastatic competence upon disseminating HCC cells (12).

The study by Ai et al. (12) ascribes novel functions to pIgR but also raises intriguing questions that warrant further investigation: 1) Given that pIgR is expressed on the surface of several glandular epithelia, including those of the liver, intestine, and breast (14), does pIgR activation play similar roles in other carcinomas known to be exacerbated by inflammation? 2) Is the expression of pIgR necessary for TGF-β-induced EMT? 3) How does pIgR modulate the transcriptional output of Smad signaling? 4) Given that Smad2/3 and pIgR interact at the early endosome, does the entire pIgR-Smad complex translocate to the nucleus and participate in target gene regulation? Or, does Smad4 displace pIgR from the pIgR-Smad complex before nuclear translocation? 5) Given that pIgR potentiates Smad-mediated EMT through a physical interaction with Smad2, does pIgR activation affect Smad-independent noncanonical TGF-β...
signaling cascades (18)? 6) Which kinases and/or phosphatases regulate pIgR activation, in response to inflammation, thus influencing Smad recruitment and downstream signaling? 7) What additional proteins—if any—comprise the pIgR-Smad complex (eg, SARA, Smad4) (16,19)? 8) Is pIgR-Smad complex formation necessary for the EMT programs induced by other inflammatory cytokines?

Furthermore, although Ai et al. (12) demonstrate the enhanced colonization ability of pIgR-overexpressing cells when introduced via injection into the tail vein, additional experiments are necessary to determine its effects on spontaneous metastasis originating from orthotopic or autochthonous tumor models. The generation of mouse models specifically and temporally expressing pIgR in the liver or, indeed, knock-in mice in which pIgR activation is disrupted by mutation of serines S682 and/or S734 (to alanine) will be useful to investigate the pathogenic consequences of pIgR-mediated EMT in distinct liver cell types in situ. Moreover, examining the relevance of pIgR in established models of HCC and liver fibrosis (eg, bile duct ligation, carbon tetrachloride) will enable lineage tracing and serve to determine whether pIgR-expressing cell types may contribute to liver disease, be it fibrosis or malignancy. Importantly, given that HCCs are highly resistant to chemotherapy (3,20) and EMT has been linked to increased liver cell survival post-cytotoxic insult (20), such tractable models will address whether and how pIgR inhibition may modulate resistance to therapy.

Given the recently established connection between EMT and stem cell properties (21,22), the findings of Ai et al. (12) raise the intriguing possibility that pIgR may also affect stemness. This is especially important in view of the emerging literature on the roles of EMT and stem cells in HCC progression, heterogeneity, and resistance to therapy (20,23–25).

A key finding of this study (12) is that different and separable portions of pIgR are important in mediating its transctytosis functions and the induction of EMT through the recruitment of R-Smads. Thus, mutations in tyrosine and serine residues (Y677F and Y743F, S673A, and S735A) that are important for transctytosis do not seem to affect pIgR-induced EMT, but mutations in two serine residues (S682A and S734A) unrelated to transctytosis attenuate the ability of pIgR to elicit EMT. These results may guide the development of therapies specifically directed toward the inhibition of pIgR-elicted EMT without affecting its roles in transcytosis. Thus, treatment strategies directed at inhibiting pIgR may help curbf recurrent HCC or metastasis following tumor resection and may improve patient responsiveness to immune-based therapies as they may alleviate the immunosuppressive effects of TGF-β.

Whether inhibiting pIgR can indeed be achieved without eliminating its functions in transctytosis and antigen presentation and whether such agents will interfere with the physiological roles of TGF-β in normal tissue homeostasis or the immune system remains to be seen.

References


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